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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,561	08/25/2003	Michael David Bentley	034848/268660	3230

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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/647,561	BENTLEY ET AL.	
	Examiner	Art Unit	
	THOMAS S. HEARD	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-16,18,19,23,24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-16,18,19,23,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Applicants Amendments to the claims received on 1/14/2010 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 7/14/2009 are hereby withdrawn.

Claim(s) 1-3, 6-16, 18, 19, 23, 24, 26, and 27 are pending. Claim(s) 24 are withdrawn. Claims 1-3, 6-16, 18, 19, 23, 26, and 27 are hereby examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. V. Quigg, 14

USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976);In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

Claims 1-3, 6-16, 18, 19, 23, 26 and 27 rejected under 35 U.S.C. 103(a) as being unpatentable over

Abbruscato TJ, et al, "Blood-to-central nervous system entry and stability of biphalin, a unique double-enkephalin analog, and its halogenated derivatives," J Pharmacol Exp Ther. 1996 Mar;276(3):1049-57 and

Delgado C, Francis GE, Fisher D., "The uses and properties of PEG-linked proteins," Crit Rev Ther Drug Carrier Syst. 1992;9(3-4):249-304 (made of record in the previous office action), **or**

Ekwuribe et al, WO 01/19406.

The instantly claimed invention is drawn to a hydrophilic polymer-peptide conjugate consisting of a peptide that is either biphalin (Applicant's elected species) or [D-Pen2, D-Pens] enkephalin (DPDPE) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol, wherein said conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier

Abbruscato TJ, et al teaches the blood to CNS entry and stability of biphalin. Abbruscato teaches that after systemic administration only a small amount of biphalin was detected in the brain, but analgesia was detected, teaching that biphalin is capable of entering the CNS. Abbruscato et al teaches that improved CNS entry of a biphalin analog, that of a chlorohalogenated biphalin was achieved due to enhanced lipophilicity and through enhanced stability., see abstract, and page 1050, column 1 and third paragraph. Abbruscato et al teaches that this study which incorporated chlorohalogens into biphalin is a promising structural modification in the development of biphalin as a successful opoid drug to the clinic, see abstract. Abbruscato et al does not teach the pegylation of biphalin for improved stability or improved CNS uptake.

Delgado et al teaches the beneficial uses and properties of PEG-linked proteins and peptides. Delgado et al et al teaches that the addition of the Peg adds both hydrophobic (lipophilic) and hydrophilic properties to the PEG conjugated peptide. Delgado et al teaches a wide range of benefits of PEGylating a protein which are 1) increased plasma half-life, 2) reduced renal clearance, 3) reduced cellular clearance, 4) reduced proteolysis, 5) reduced immunoclearance, 6) reduced immunogenicity and antigenicity, and 7) increased solubility, among 8) other properties of the PEG-protein conjugates. Unrelated PEG-proteins are shown to have these beneficial properties demonstrating the broad acceptance of the conjugated PEG to the proteins, and that the PEG is determining the property. Delgado et al further teaches mono-pegylation, bi- and multiple-pegylation, N-terminal PEGylation and PEGylation in ranges from 700 to 70,000

MW readable upon PEG ranging from 10 to 2000, readable on Claims 3, 6-10, 11-16, 18-19, 26, and 27. Note that in Claim 3 is a negative limitation that is readily apparent in the examples of Delgado et al, see Figure 3 for example. The linkage to the Tyrosine as claimed in Claim 19 would be at the N-terminus because the Tyrosine is the N-terminal amino acid and meets the limitation of those Claims 19 as well as Claim 6 and 7. Delgado et al teaches a plurality of different PEG moieties readable upon co-polymers of Claim 8 as well as polyethylene glycol of Claims 1, 6, 7, 10-18, 19, 26, and 27.

Ekwuribe et al teaches the conjugating of PEG to a drug to make a prodrug that is capable of crossing the blood brain barrier (BBB). On page 11 of the WO document, for a PEG conjugated drug molecule, PEG can both increase lipophilic or hydrophilic properties of the attached drug. The PEG also functions to enhance the delivery of compounds that can enter the CNS via the BBB, or deliver compounds that cannot otherwise be delivered through the BBB into the CNS. Ekwuribe et al, therefore, adds yet another beneficial property of PEG to the attached drug, to those already related in the Delgado et al reference supra.

It would have been obvious to one of ordinary skill in the art to PEGylate neuropeptide biphalin as taught by Delgado et al, in substitution for the chlorohalogenation taught by Abbruscato et al for the common purpose of increased stability of the peptide. One would have been motivated to do so given that Delgado et al teaches improved pharmacokinetic profiles for peptides and proteins that are PEGylated. The improved pharmacokinetics of PEGylated proteins taught by Delgado come from increased plasma half-life, reduced renal

clearance, reduced cellular clearance, and reduced proteolysis. Because one would expect greater stability of the PEGylated biphalin peptide, one would also expect an improvement of the PEGylate biphalin to cross the BBB given that stability was one of the contributing factors in the increased CNS uptake of biphalin as taught by Abbruscato et al, and pegylation of proteins and peptides provides this property. One would have had a reasonable expectation of success in Delgado et al teaches that PEGylating peptides is routine, that such PEGylation provides improved performance in at least eight (8) areas important in pharmacology, and that these improved properties are not protein dependent. Additionally, one would have been motivated to PEGylate the biphalin because Ekwuribe et al teaches that pegylating drugs add an additional property of allowing the drug to be transported across the BBB. Note that Claims 1 and 2 are claims to results that are the effective outcome of PEGylating a protein and would necessarily follow upon pegylation of biphalin, that of the ability to cross the BBB.

From the teachings of the references supra, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention, that of pegylating a neuropeptide. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, and the invention as claimed, is rejected under 35 U.S.C. 103(a).

Applicant's Arguments

Rejection 1. Abbruscato combined with Delgado: First, in examining Abbruscato, this reference, even when combined with Delgado, fails to suggest the subject matter of the instant claims, and in fact, teaches away from them. Specifically, Abbruscato teaches that in order to improve passive passage across the BBB over an unmodified drug such as biphalin, one must enhance the drug's lipophilicy. The instant claims recite just the opposite - i.e., a polymer-peptide conjugate that itself is hydrophilic and also capable, when administered into the blood circulation, of transport across the BBB. In no way would one skilled in the art, based upon the teachings of Abbruscato, expect a hydrophilic conjugate of biphalin to cross the BBB. The data shown in Fig. 3 of the Applicants' specification, i.e., that exemplary hydrophilic conjugates having the features recited in the claims exhibit improved analgesia over unmodified biphalin, is absolutely unpredictable based upon the teachings of Abbruscato.
In sum, the combination of Abbruscato and Delgado fails to render obvious the instant claims, since the combination fails to even remotely suggest the subject matter recited in the claims, and in fact, teaches the exact opposite.

Rejection 2. Ekwuribe: Turning now to Ekwuribe, this reference has no bearing on the patentability of the instant claims. Recalling the requirement to review the art as a whole, the conjugates of Ekwuribe are completely dissimilar from the conjugates recited by the Applicants. Ekwuribe describes amphiphilic prodrugs having small oligomeric PEGs covalently attached thereto. In contrast, the instant claims are directed to hydrophilic conjugates having significantly larger polyalkylene oxide chains attached thereto (having a molecular weight from about 2,000 to about 100,000 daltons). Finally, Ekwuribe suggests that an active transport system is required to facilitate transport of a hydrophilic drug across the blood brain barrier. The claimed conjugates lack such a transport system, as has been pointed out by the Applicant's on numerous prior occasions over the course of prosecution. That is to say, nowhere does Ekwuribe suggest or lead one of skill in the art to the subject matter embodied in the Applicants' claims.

In view of the above, it is submitted that the pending claims are non-obvious and comply with the standards of 35 U.S.C. §103. Withdrawal of the rejections of the claims under 35 U.S.C. §103 is therefore respectfully requested.

Response to Applicants Arguments

Applicants arguments have been carefully considered but are not deemed persuasive to overcome the rejection.

First, regarding (1), the reason to PEGylate is well known in the art, and the Delgado et al reference provided eight (8) reasons to motivate one of ordinary skill in the art to PEGylate a therapeutically active. Protein. The reason or motivation to PEGylate a given protein need not be the reasons Applicants are PEGylating a protein. Abbruscato et al teaches that the increased lipophility of the conjugated biphalin was the reason for increased BBB crossing –not biphalin is already capable of crossing the BBB, albeit less that biphalin that is PEGylated. Delgado et al teaches that PEG adds both hydrophobic (lipophilic) and hydrophilic properties to the PEG conjugated peptide, and these properties are the reason for increased BBB crossing, also taught by Ekwuribe et al. There is plenty of motivation to PEGylate a protein from the single reference of Delgado et al alone. Given that Delgado et al teaches that PEG adds both hydrophobic (lipophilic) and hydrophilic properties to the PEG conjugated peptide rebuts the arguments from Abbruscato et al.

Regarding (2), the fact that Ekwuribe et al teaches the conjugation of PEG to a non-peptide compound is not a reason for one of ordinary skill in the art to not adhere to the teaching of the reference. Applicants have stated that the reference lacks the teaching of BBB transport, stating that this has been argued *throughout* the prosecution. This statement is not clear, nor is the argument that an active transport system must be in place for the BBB transport. Ekwuribe et al reference has only been used once in the prosecution, and that was in the previous office action. Further, Ekwuribe et al states in the Abstract and through out the document, that conjugation of PEG to the compound achieves the

desired BBB transport property. How it crosses the BBB is not important. The fact that it does is enough to motivate one of ordinary skill in the art to modify the molecule that one wants to bring across the BBB with PEG. PEGylation is the modification to the biologically active molecule, and the teachings of Ekwuribe et al adds one more motivation to those taught by Delgado et al to PEGylate a molecule one wants to target across the BBB.

From the teachings of the references supra, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention, that of pegylating a neuropeptide. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, and the invention as claimed, is rejected under 35 U.S.C. 103(a).

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Prior art contained in the reference of record can be applied in the next office action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted

that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas S. Heard** whose telephone number is **(571) 272-2064**. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thomas S Heard/
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654